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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/485,245	03/27/2000	ALISON HOPKINS	28911/36128	1697
<div>7590 12/26/2006 MARSHALL O'TOOLE GERSTEIN MURRAY &amp; BORUN 6300 SEARS TOWER 233 SOUTH WACKER DRIVE CHICAGO, IL 60606-6402</div>			<div>EXAMINER WILDER, CYNTHIA B</div>	
			ART UNIT	PAPER NUMBER
			1637	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		12/26/2006	PAPER	

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

**Office Action Summary**

Application No.

09/485,245

Applicant(s)

HOPKINS, ALISON

Examiner

Cynthia B. Wilder, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 20 November 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 7-14 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 7-14 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114 was filed in this application after a decision by the Board of Patent Appeals and Interferences, but before the filing of a Notice of Appeal to the Court of Appeals for the Federal Circuit or the commencement of a civil action. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on November 20, 2006 has been entered.

2. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). Claims 1-6 have been canceled. Claims 7-14 are pending and addressed in this Office action.

#### ***Previous Rejection***

The claim rejection under 35 USC 112 second paragraph is withdrawn by the Examiner in the Examiner Answer filed on 12/1/2005. The prior art rejection under 35 USC 103(a) directed to claims 7-14 is maintained. The new matter rejection under 35 USC 112 first paragraph directed to claims 7-10 is maintained.

***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Once again, claims 7-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Godiska et al. (5,759,804, filed November 17, 1993) in view of Shen et al. (EP 0 726 310 A1 February 09, 1996). Regarding claims 7-14, Godiska et al teach a method comprising a random mixture of oligonucleotides which are 6-mers, wherein the composition further contains at least a supply of nucleotides for chain extension, a labeled nucleotide, and a polymerase enzyme (col. 8, lines 27-31). Godiska et al differs from the instant invention in that Godiska et al do not expressly teach wherein the solution comprising the random mixture of 6-mers is in a freeze-dried state. Shen et al teach a method and composition similar to that of Godiska et al, wherein said composition is present in a dry state (page 4, lines 37-41). Shen et al teach wherein the composition may comprise primers, a polymerase enzyme, a supply of nucleotides for chain extension, and a stabilizer (page 6, lines 3-7 and 22). Shen et al teach that the composition present in the dry state is advantageous because the composition is stable for a prolonged period, even when stored at high temperature. Shen et al further teach that a composition in a dried state is useful in shipping and storage of commercial preparations for use in e.g., nucleic acid amplification kits (page 6, lines 39-41). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have been motivated to have provided the random mixture of 6-mers in the method as taught by Godiska et

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al in a dried state for the advantage taught by Shen et al that a nucleic acid composition (such as primers) present in a dried state is useful in shipping and storage of commercial preparations due its increase stability, even when stored for prolonged periods or when stored at high temperatures.

***Claim Rejections - 35 USC § 112 first paragraph: New Matter***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Once again, claims 7-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a method of forming a random mixture of oligonucleotides which is resistant to self-annealing comprising the steps of selecting a random mixture of oligonucleotides which are 6-mers to 8-mer and drying said mixture. Applicant provides no cited support for the new limitation "oligonucleotides which is resistant" and thus a review of the specification as originally filed does not support or depict what is claimed. While the specification illustrates as a group a reduction in the percent (%) of self-priming when utilizing mixtures of oligonucleotides which are 6-mer to 8mers versus oligonucleotides which are 9-mers, there is no disclosure which illustrates whether or not the reduction in % of self-priming is due to a "selection process" of oligonucleotides having a self annealing resistant

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property or whether or not the reduction in % self-priming is due to an interaction between the random oligonucleotides or whether or not the reduction in the % of self priming is due the sequences of the oligonucleotides. No support has been found anywhere in the specification which suggests that the oligonucleotides of the invention are "resistant" to self-priming or "resistant" to self-annealing. Therefore, the specification would not have suggested to the skilled artisan that the Applicant was in possession of the claimed invention as of filing date.

***Applicant's traversal***

7. Applicant traverses the rejection on the following ground: Applicant states that the application Examples demonstrate a critical and unexpected difference in self-priming activity and labeling intensity between 6-8 mers and 9-mers and there is no teaching in the art that such a difference could occur. Applicant states accordingly, the obviousness rejection should be withdrawn because the art fails to teach the desirability of short primers in a dried primer system or that 6-mer to 8-mers would behave differently with respect to self-priming activity and labeling intensity than do 9-mers. Applicant states that more specifically, Godiska discloses liquid 6-mers but fails to teach that the selection of 6-mers to 8-mers constitutes a critical range or that short primers would be desirable in a dried primer system. Applicant state while Godiska discloses a random mixture of 6-mers and other ingredients the Examiner acknowledges that Godiska does not teach a labeling composition in a dried state. Applicant states that moreover, there is nothing in Godiska that teaches that the selection of 6-mers to 8-mers is important in either the liquid or freeze-dried state to reduce self- annealing. Applicant states that in fact, self-annealing is not mentioned at all.

Applicant asserts that in addition, Shen discloses 48-mer and 22-mer primers and fail to suggest that dried primers should be shortened or alternatively any reason why the primers of Godiska should be dried. Applicant states that this is because the prior art generally taught that longer primers were preferred because longer primers have higher melting temperatures and are this more specific. Applicant states that moreover, Shen acknowledged that "whether a particular composition will function to preserve biological activity for a particular biologically active material is not a priori predictable and only discloses freeze-drying as an option and in addition, Shen fails to provide any reason why the primers of Godiska should be dried given the fact that shorter primers were thought to be inherently more stable and there was no reason to believe that the shorter Godiska primers would benefit from being in a freeze dried kit.

Applicant states that the Board rejected these arguments on the basis that Applicants showing of unexpected results was insufficient to rebut a *prima facie* case of obviousness because the closest prior art to dried 6-mers primers is not dried nanomers, but random 6-mer primers that have not been dried, as taught by Godiska. Applicant states that this argument is incorrect because the closest prior art to dried 6-mers is dried 9-mers! Applicant states that because the rejection is an obviousness rejection, the closest prior art is the prior art that those of ordinary skill in the art would consider most relevant and would have been most motivated to practice. Applicant states that for the reasons set out above, the bias in the art was toward longer rather than shorter primers at the same time, it taught dried primers rather than primers in solution. Applicant contends that the person of ordinary skill in the art would have been motivated to modify the short wet primers of Godiska to the long dry primers of Shen, not the short dried primers of the invention. Applicant states that because the claimed invention is

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unobvious over what was taught by the prior art and preferred by those of skill in the art at the time of Applicant's invention, it is neither necessary nor appropriate to make comparisons over different compositions that were not preferred by the art. Applicant concludes that the rejection should be withdrawn.

***Examiner's Response***

8. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons that follow: In response to Applicant's arguments that the instant invention demonstrates the critical and unexpected differences in self-priming activity and labeling intensity between 6-8 mers and 9 mers, the Examiner maintains that the claims as broadly written do not describe or recite any steps, characteristics or improvements which distinguishes Applicant's invention over the teachings of the prior art. The Examiner agrees with Appellant that the art teaches the use of random primers collections of various lengths in random priming methods and the use of dried primer kits that contain long primers, such as dried 15-17-mers. However, the examiner disagrees that the instant invention, specifically the Examples 2 and 4 demonstrates a critical difference in self-priming activity and labeling intensity between short dried 6-8 mers which resist self-annealing compared with longer long dried 9-mers and above. In fact, contrary to Applicant arguments, the specification specifically the examples 2 and 3 do not depict any resistance of self-annealing when using primers 6-8 mers in DNA labeling experiments but rather shows a reduction in self-annealing (self-priming). The Example 3 depicts the percent incorporation of 6-mer primers taken from the average of two reactions versus the percent incorporation of 9-mer primers taken from a single experiment. The specification specifically states that "the results obtained in the Example 3 were obtained using



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wet reagents", but *speculates* that "the conclusion would apply also when dried primers are used" (see specification page 10, lines 8-9). Again, the Example 3 does not depict any resistance to self-annealing or self-priming as argued by Appellant and additionally does not show the criticality of random hexamer versus nanomer in a dried state.

In response to Appellants arguments against the references of Godiska and Shen individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, the primary reference of Godiska et al., is cited for its teaching of a method comprising a random mixture of 6-mers oligonucleotide as required by the claims 7, 10, 11 and 14 and reagents for a chain extension assay as required by claims 9 and 13. As stated in the prior Office, Godiska et al do not expressly teach wherein the 6-mers are in a dried state. However, this limitation is provided in the teachings of the secondary reference by Shen. Shen et al teach a method and composition comprising primers in a dried state and reagents for chain extension as required by claims 7-8, 11 and 12. Shen provides motivation for providing the primer and other reagents required for chain extension in a dry state. Shen et al teach that a composition, comprising primers and reagents in a dried state is advantageous because the composition is stable for a prolonged period, even when stored at high temperature. Shen et al further teach that a composition in a dried state is useful in shipping and storage of commercial preparations for use in e.g., nucleic acid amplification kits (page 6, lines 39-41). Thus, the combined teaching of Godiska et al in view of Shen et al establishes a case of obviousness over the instant invention. MPEP 8<sup>th</sup> edition states that "[T]he test for obviousness is not whether the features of a

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secondary reference may be bodily incorporated into the structure of the primary reference....Rather, the test is what the combined teaching of those references would have suggested to those of ordinary skill in the art " *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). See also *In re Sneed*, 710 F.2d 1544, 1550, 218 USPQ 385, 389 (Fed. Cir. 1983) ("[I]t is not necessary that the inventions of the references be physically combinable to render obvious the invention under review."); and *In re Nievelt*, 482 F.2d 965, 179 USPQ 224, 226 (CCPA 1973) ("Combining the teachings of references does not involve an ability to combine their specific structures"). The Board affirms the Examiner's rejection and states that "the motivation to combine references does not have to be identical to that of appellant to establish obviousness." See *In re Kemps*, 97 F.3d 1427, 1430, 40 USPQ2d 1309, 1311 (Fed. Cir. 1996). The Board reiterates the Examiner's rejection and states that Godiska is cited for its teaching of a priming reaction using random 6-mer primers. The Board states that although Shen does not teach 6 mers to 8 mers random primers, Shen teaches the desirability of providing dried reagents.

In regards to Applicant's arguments that the basis of the board rejection concerning Applicant's showing of unexpected results is incorrect, the Examiner respectfully disagree. At page 8 of the decision by the Board, the Board states,

"[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art," *In re Baxter Travenol Labs.*, 952 F.2d 388, 392, 21 USPQ2d 1281, 1285 (Fed. Cir. 1991), citing *in re De Blauwe*, 736 F. 2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984). The Board states that we find that the closest prior art is not dried 9-mers, but random 6-mers primer that have not been dried as taught by Godiska."

It is clear from the Board's decision that they are referring to a comparison between the claimed language which recites "a random mixture of oligonucleotide which are 6-mer to 8-

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mers" and the closest prior art, which is a random mixture of oligonucleotides that are 6-mers that have not been dried. Contrary to Applicant's arguments, the closest prior would not be dried 9-mers because the random mixture as claimed by Applicant is directed to a composition of random oligonucleotides having specific length limitations. The freeze-dried property of the composition is a secondary factor of Applicant's invention as Applicant teaches in the Example 3 wherein results are obtained using wet reagents of the random oligonucleotide composition, not freeze-dried.

Nonetheless as noted by the Board and the Examiner, the secondary reference of Shen provides motivation and the desirability of providing primers in a freeze-dried state, which would have been obvious to one of ordinary skill in the art at the time of the claimed invention. To reiterate, it would have been *prima facie* obvious to one of ordinary skill in the art to dry the reagents of Godiska as taught by Shen to achieve the advantages of Shen of being useful in shipping and storage of commercial preparation due to increased stability, even when stored for prolonged periods or when stored at high temperatures.

Applicant's arguments are not sufficient to overcome the prior art rejections under 35 USC 103(a). Accordingly, the rejections are maintained.

### ***Conclusion***

3. No claims are allowed. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

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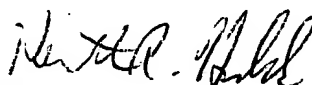
the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

cbw

  
KENNETH R. HORLICK, PH.D.  
PRIMARY EXAMINER

12/18/06